Monday, March 4, 1991
2:00PM–3:30PM, Room 215, East Concourse
New Metabolic Insights into Myocardial Injury Cardiac Metabolism of Myocardial Ischemia and Injury

2:00
EFFECT OF ADENOSINE RECEPTOR BLOCKADE OR TRANSPORT INHIBITION ON POSTISCHEMIC METABOLIC AND FUNCTIONAL RECOVERY IN RAT HEART

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This study evaluated whether modulation of endogenously-released adenosine by either blockade of adenosine receptors with 8-phenyltheophylline (8PT) or inhibition of adenosine transport with nitrobenzylthioinosine (NBMPR) affects high energy phosphate metabolism and function during ischemia (I) and reperfusion (R). Isolated rat hearts crystalloid-perfused at constant flow were subjected to 30 minutes each of low-flow I (0.5 ml/min) and R to baseline flow (9 ml/min). Infusion of vehicle control (C, n=7), 8PT (10μM, n=6), or NBMPR (10μM, n=5) was begun 10 minutes prel and maintained through I and R. ATP, Phosphocreatine (PCr) and inorganic phosphate (P_i) were assessed using ^{31}P-NMR spectroscopy. Function is represented by heartrate-systolic pressure (HR-SDP) product. Neither drug nor C infusion affected baseline function or metabolism. During I all groups had a significant functional deficit but NBMPR-treated hearts had better function than C or 8PT hearts. During I and R, 8PT and NBMPR had significantly different effects on metabolism:

Drug	Period	ATP	PCr/P_i	HR·SDP
Control	I	73±3	13±1	44±1
	R	90±4	109±2	108±8
8PT	I	73±5	15±1	56±3
	R	84±3	26±2**	104±2
NBMPR	I	82±5	26±3	10±1*
	R	88±3	56±3+	110±14

values are % baseline, mean ± SEM: **, *, + p<.05 vs C or 8PT.

ATP values were not significantly different between groups. During I, the PCr/P_i ratio was higher in NBMPR hearts. During R, 8PT and NBMPR hearts had lower PCr/P_i than C, but NBMPR had higher PCr/P_i than 8PT hearts. Early post I, purine efflux was reduced in NBMPR hearts (950 pmoles/ml ±100) and enhanced in 8PT (2100 pmoles/ml ±500) compared to C hearts (1500 pmoles/ml ±200); p<.05. Total Purine efflux during R was elevated in 8PT and NBMPR (327±113 and 214±72 nmoles) vs. C hearts (127±28 nmoles) (p<.05). Thus, inhibition of purine loss during ischemia improves ischemic function and metabolism, but during R, enhanced purine efflux or adenosine receptor antagonism is detrimental to metabolism.

2:15
PARTIAL CORONARY OCCLUSION IS ASSOCIATED WITH DEPLETION OF TISSUE OXYGEN STORES.

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The relationship of myocardial blood flow to transmural changes in tissue oxygenation was assessed using near infrared (NIR) spectroscopy. In 7 open chest dogs, partial LAD occlusion (PO) produced a drop in coronary blood flow, tissue oxygen stores ($tHbO_2$ + MbO_2), tissue blood volume (tBV), and the oxidation level of mitochondrial cytochrome a,a_3. Mean transmural blood flow, measured by radiolabelled microspheres, decreased from a control level of 0.93 ± .17 to 0.45 ± .17 ml/min/gm (p<.001), and myocardial oxygen consumption (MVO_2), measured by Fick using venous blood from the great cardiac vein, decreased from 8.5 ± 2.7 to 4.7 ± 1.6 $ml O_2$/min/100gm (p=.003). Complete occlusion (CO) produced greater decreases in myocardial blood flow (0.23 ± .15 ml/min/gm, p=.004 vs PO), MVO_2 (2.4 ± 1.6 $ml O_2$/min/100gm, p=.002 vs PO), tBV (p=.001 vs PO), and the cyt a,a_3 oxidation level (p=.003 vs PO), but no further decrease in the tissue O_2 store (p=.60 vs PO). Complete tissue deoxygenation at death led to an additional decline in the oxidation state of cyt a,a_3 (p=.01 vs CO), without further decrease in the tissue O_2 store. These results indicate that as little as a 52% reduction in myocardial blood flow below preischemic levels produces essentially complete depletion of the tissue O_2 store. Therefore, under conditions of restricted blood flow and limited oxygen supply, myocardial tissue becomes "storeless". The storeless state is characterized by rapid mitochondrial extraction of all available O_2 and, notably, the absence of detectable O_2 accumulation in tissue hemoglobin or myoglobin.

2:30
PRODUCTION OF INTERLEUKIN 6 BY ATRIAL MYXOMAS MAY EXPLAIN SYSTEMIC SYMPTOMS

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To precise the possible relation between systemic features and atrial myxomas (AM), we realised IL6 studies of 22 cases of AM. IL-6, a pleiotropic cytokine involved in inflammatory processes and autoimmune diseases, has been demonstrated to be produced by AM. Constitutional symptoms (CS) present in 12 patients disappeared after removal of the AM. No recurrence and normal serum IL6 values at follow-up (mean = 5.2 yrs) suggest that CS are not due to a systemic response to tumor necrosis breakdown products. IL6 dosages were obtained in the serum pre- and postoperatively and from the supernatant of confluent tumor cells in culture in 4 cases. One patient, with inflammatory and immune features, produced 14-22 fold higher IL-6 values than the 3 others and was the only one with systemic passage of IL-6 with IL-6 levels (56 pg/ml) beyond those observed in patients with rheumatoid arthritis. This patient presented also an IL-6-dependant proliferative polyclonal plasmacytosis in the bone marrow. After surgical removal of the AM, serum IL-6 and CS disappeared. These data strongly suggest that the overproduction of IL-6 with a systemic passage can be responsible for the inflammatory and immune features observed in AM and similar to autoimmune diseases.

2:45
FATTY ACID KINETICS IN AEROBIC MYOCARDIUM

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The purpose of this study was to evaluate the kinetics of tracer uptake and washout to estimate carbon pool sizes (PS) within the fatty acid utilization pathway. Step-function labeling with [^{14}C]-palmitate was performed in 20 aerobically perfused, intact pig hearts. Coronary effluent was monitored for efflux of products throughout 40-60 min of perfusion. Uptake and washout analysis was expressed as:

$$PS = Q_c \times \int_0^\infty (C_{ss} - C(t)) \times dt \text{ and } PS = Q_c \times \int_0^\infty C(t) \times dt,$$

where Q_c = coronary flow, C_{ss} = steady state concentration of labeled metabolite in coronary venous blood, and C(t) = concentration of metabolite with respect to time. The only radioactive metabolites in venous effluent were fatty acids (FA) and $^{14}CO_2$. The PS of FA was small (1.2-1.7 ml/g dry wt or 0.4-0.5 μmol/g dry wt) and could be accounted for totally by substrate in the perfusate. The PS of $^{14}CO_2$ was much larger (11.4-15.8 ml/g dry wt or 3.6-4.2 μmol/g dry wt). Washout kinetics revealed that $^{14}CO_2$ production in part passed through a tissue carbon pool with a very long time constant. Counts in tissue were distributed between an aqueous soluble fraction (40%) rapidly depleted with washout and a lipid fraction (60%) which was largely contained within triacylglycerols and phospholipids. Shifts in radioactivity between the aqueous soluble fraction and complex lipids were predicted by a discrepancy between $^{14}CO_2$ production and myocardial oxygen consumption. This in turn supports the notion of a dual pathway in fatty acid oxidation, one arm of which passes through a pool with the long time constant. This pool imparts a potentially large error in estimating fatty acid oxidation by external labeling techniques with either ^{11}C- or ^{14}C-tracers.